REMARKS

Applicants wish to clarify that claims 1 and 4-7 are under active consideration while claims 2, 3 and 8-16 have been canceled (see p. 4 of the Response filed January 20, 2002). Claims 1 and 4-7 have been rejected. Reconsideration and withdrawal of the rejections set forth in the Office Action dated February 10, 2004 are respectfully requested. Applicants petition the Commissioner for a 3-month extension of time: a separate petition accompanies this amendment.

I. Amendments

Claim 1 is amended to clarify the added peptidic sequence is selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9. Support for this amendment may be found in the claims as originally filed. Applicants assert that no new matter has been added by way of this amendment.

II. Rejections under 35 U.S.C. §112, first paragraph

Claims 1 and 4-7 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1 and 4-7 were further rejected under 35 U.S.C. §112, first paragraph, allegedly because the specification does not enable a person skilled in the art to which it pertains, or with which it is most connected, to make and use the invention commensurate in scope with the claims.

These rejections are respectfully traversed.

A. Written Description

Claims 1 and 4-7 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The claims, as amended, are directed to an antigen composition capable of eliciting an enhanced cytotoxic T cell response in the context of a major histocompatability complex class I

molecule (MHC class I), comprising an antigen having an added peptidic sequence selected from the group consisting of SEQ ID NO:1-9.

The specification describes peptidic sequences that can be linked to an antigen such that the antigen is capable of triggering naïve cytotoxic T lymphocyte responses *in vivo* on page 7, lines 29-36. The specific sequences of SEQ ID NO:1-9 are provided in Table 1 on page 16.

Further, According to MPEP (II)(A)(3)(a), possession of the claimed invention may be shown by describing an actual reduction to practice. As described in Example 2 (see page 17), Applicants prepared various OVA-peptide conjugates inlcuding OVA-pK (SEQ ID NO:1) and OVA-pEA (SEQ ID NO:2). Dendritic cells (DC) were pulsed with either OVA alone or OVA-pEA/pK and injected into mice. Applicants found that OVA conjugated to pEA/pK elicits an effective CTL response. As shown in Fig. 4, mice primed with DC previously pulsed with OVA conjugated to pEA/pK generated significant CTL responses against OVA-transfected target cells (E.G7-OVA), while the corresponding response in mice immunized with OVA-pulsed DC alone was substantially lower.

Accordingly, Applicants submit that these teachings in the specification show that Applicants had possession of the invention as presently claimed at the time of filing.

B. Enablement

The first paragraph of 35 U.S.C. §112 requires that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention without undue experimentation (e.g., *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir., 1991).

The enablement requirement is met if the description enables any mode of making and using the claimed invention (*Engel Industries, Inc. v. Lockformer Co.*, 946 F.2d 1528, 20 USPQ2d 1300 (Fed. Cir. 1991).

Claim 1, as amended, specifies that said added peptidic sequence that facilitates entry of said antigen into said APC consists of one of SEQ ID NO:1-9. As noted by the Examiner, the specification is enabling for making and/or using a composition comprising an antigen and an added peptidic sequence selected from the

group consisting of SEQ ID NO:1-9, which facilitates entry of an antigen into an APC (see Office Action dated February 10, 2004; page 4). The specification discloses how to make and use the instant invention wherein the added peptidic sequence is selected from the group consisting of SEQ ID NO:1-9. Accordingly, Applicants submit that one of skill in the art would be enabled to make and use the presently claimed invention. In view of the above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

III. Rejections under 35 U.S.C. §103

Claims 1 and 4-7 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Buschle *et al.* (PNAS USA 94:3256-3261, (1997)) in view of Kim *et al.* (J. Immunol 159(4):1666-1668, (1997)). This rejection is respectfully traversed for the following reasons.

A. The Invention

The present invention relates to an antigen composition comprising an antigen having an added peptidic sequence selected from the group consisting of SEQ ID NO: 1-9, which facilitates entry of the antigen into antigen presenting cells. The composition is capable of eliciting an enhanced cytotoxic T cell response in the context of a major histocompatibility complex class I molecule (MHC class I) as the peptidic sequence facilitates entry of the antigen into antigen presenting cells (APC).

B. The Prior Art

Buschle *et al.* disclose that polyarginine (pArg) and polylysine (pLys) enhance the uptake of peptides by APCs. Specifically, bone marrow-derived APCs were incubated with a peptide alone or a combination of labeled peptide plus pLys or pArg, and the amount of peptide transported into the APCs was measured (see pages 3258-9). Buschle *et al.* fail to disclose a composition comprising an antigen and an added peptidic sequence, wherein the added peptidic sequence is linked to the antigen, or wherein the antigen-polycationic sequence is a fusion protein. Further, Buschle *et al.* fail to show or suggest the sequences selected from SEQ ID NO:1-9.

Kim *et al.* address the problem that because exogenous proteins do not ordinarily enter the cytosol of APC and access the MHC class I-processing pathway, protein-based vaccines that induce class-restricted CTL responses have been difficult to design. A solution is to conjugate proteins such as OVA to a short cationic pepetide derived from HIV-1 *tat* (49-57 residues). Administration of the antigen/cationic peptide to APC led to processing and presentation of the peptides in association with class I MHC molecules. Thus, Kim et. al teach exposing APC to a composition containing a soluble protein conjugated to a short cationic peptide derived from HIV-1 *tat*.

C. Analysis

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. § 2143.

Determining whether a motivation to combine exists requires considering whether any of the references to be combined teach away from the claimed invention. A reference teaches away from a claimed invention if the disclosure would discourage or dissuade one skill in the relevant art from doing what the inventor actually and successfully did.

It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. *In re Wesslau*, 353 F2d 238, 241, 147 USPQ 391, 393 (CCPA 1965).

In *Bausch & Lomb v. Barnes-Hind/Hydrocurve, Inc.*, 796 F2d 443, 230 USPQ 416 (Fed. Cir. 1986), the courts stated "a reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered."

Kim *et al.* teach that a polylysine nine-mer conjugated to an antigenic peptide is ineffective to facilitate transport; thus, one of skill in the relevant art would be discouraged or dissuaded from using a polylysine nine-mer conjugated to an antigenic peptide to increase the uptake of the antigenic peptide into APCs for presentation. Thus, there is no motivation to make the combinaiton suggested by the Examiner.

The Examiner asserts that it would have been obvious to make an N-terminal cysteinylated peptide (as taught by Kim *et* al.) version of the poly-lys or poly-arg peptides of Buschle *et al.* for conjugation to an antigen, i.e., in an antigen/cationic peptide as taught by Kim *et al.*

As noted above, Buschle *et al.* disclose the ability of polylysine and polyarginine peptides to increase uptake of antigenic peptides into antigen presenting cells. In the teaching of Buschle *et al.* the polylysine and polyarginine are co-incubated with the antigenic peptide; that is, the polylysine and polyarginine are not conjugated to the antigenic peptide.

The Examiner looks to Kim *et al.* to provide the feature of joining or "adding" the peptide to the polylysine or polyarginine to the antigenic peptide. As noted above, Kim *et al.* describe modifying the antigenic peptide OVA with a cysteine and a three-alanine spacer for conjugateion with the heterobifunctional cross-linker maleimidobenzoyl-N-hydroxysulfosuccinimide ester (page 1666, Col. 2, materials and methods section), which is then linked to *tat* (RKKRRQRRR). In fact, Kim *et al.* describe the antigenic peptide OVA modified by conjugation to a peptide of nine lysines (page 1667, Col. 2, first full paragraph). According to Kim *et al.*, the polylysine peptide of nine residues was chosen as "a control to demonstrate that neither the addition of a heterobifunctional cross-linker nor a highly positive charged peptide was sufficient for transport" (page 1667, Col. 2, first full paragraph). Kim *et al.* show in Fig. 1 that uptake of the antigenic peptide OVA was specifically the result of the *tat* peptide and not due to the heterobifunctional cross-linker or the addition of a polycation, since the target cells failed to present OVA conjugated to polylysine (Fig. 1; (page 1667, Col. 2, first full paragraph).

Thus, Kim *et al.* show that the antigenic peptide OVA when conjugated to a nine-residue polylysine fails to cause uptake of the antigenic peptide into APCs for presentation. In light of this teaching, Applicants fail to see how one of skill in the relevant art would be motivated to take the teaching from Kim *et al.* of conjugation of a peptide to the antigen OVA, since Kim *et al.* show that the result of enhanced APC uptake of an antigenic peptide is specific to modification of the antigenic peptide with *tat*, and that modification with polylysine does not work. The Kim *et al.* reference "teaches away" from Applicants' claimed invention. Applicants submit that one of skill

would read the combined teachings of Buchle *et al.* and Kim *et al.* to suggest that enhanced uptake of an antigenic peptide into APCs can be achieved by (1) co-incubation of the antigenic peptide with a polycationic peptide sequence (as taught by Buchle *et al.*) or (2) modification of the antigenic peptide with *tat*, but that modification of the antigenic peptide with a polycationic sequence will not improve uptake (as taught by Kim *et al.*). In contrast to the teaching in Kim *et al.*, Applicants have clearly shown that the peptide sequences identified by SEQ ID NOS:1-9 improve uptake of an antigenic peptide from OVA into APCs (see Examples 1, 2). Thus, Applicants have asserted a discovery beyond what was known to the art.

Therefore, because the combined teachings of Buchle *et al.* and Kim *et al.* fail to show or suggest the specific peptidic sequences presently claimed, or that such peptidic sequences when added to an antigen would be able to facilitate entry of the antigen into APCs, the claims are not rendered obvious by these teachings. Withdrawal of the rejection is therefore respectfully requested.

IV. Conclusion

In view of the foregoing, Applicants submit that the claims pending in the application are in condition for allowance. A Notice of Allowance is therefore respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4360.

Respectfully submitted,
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